NIH-FDA Pediatric Drug Development Process

FDA Stakeholders Meeting

March 25, 2015

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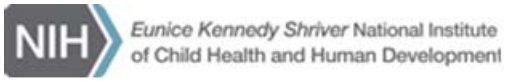


Pediatric Drug Development: The Best Pharmaceuticals for Children Act

NIH Role

- Prioritize therapeutic areas and therapies in need of study
- Sponsor pediatric clinical trials
- Submit data to FDA for consideration of labeling changes

Goals

- Direct
  - Pediatric labeling
  - Improving infrastructure
    - Training pediatricians and others designing and performing pediatric clinical trials
    - Creating a master contract for clinical trials performance
- Indirect
  - Increasing collaborations between NIH and FDA
  - Improving academic clinical research

2002: Master List of all Off-Patent Drugs which lack adequate pediatric labeling

Consider for prioritizing:
- Availability of S/E data
- Are additional data needed?
- Will new studies produce health benefits?
- Reformulation?

Consultation with experts in pediatric practice and research

Develop, prioritize, publish an Annual List of Drugs

2007, 2012: Therapeutic Areas

Consider for prioritizing:
- Therapeutic gaps
- Potential health benefits of research
- Adequacy of necessary infrastructure

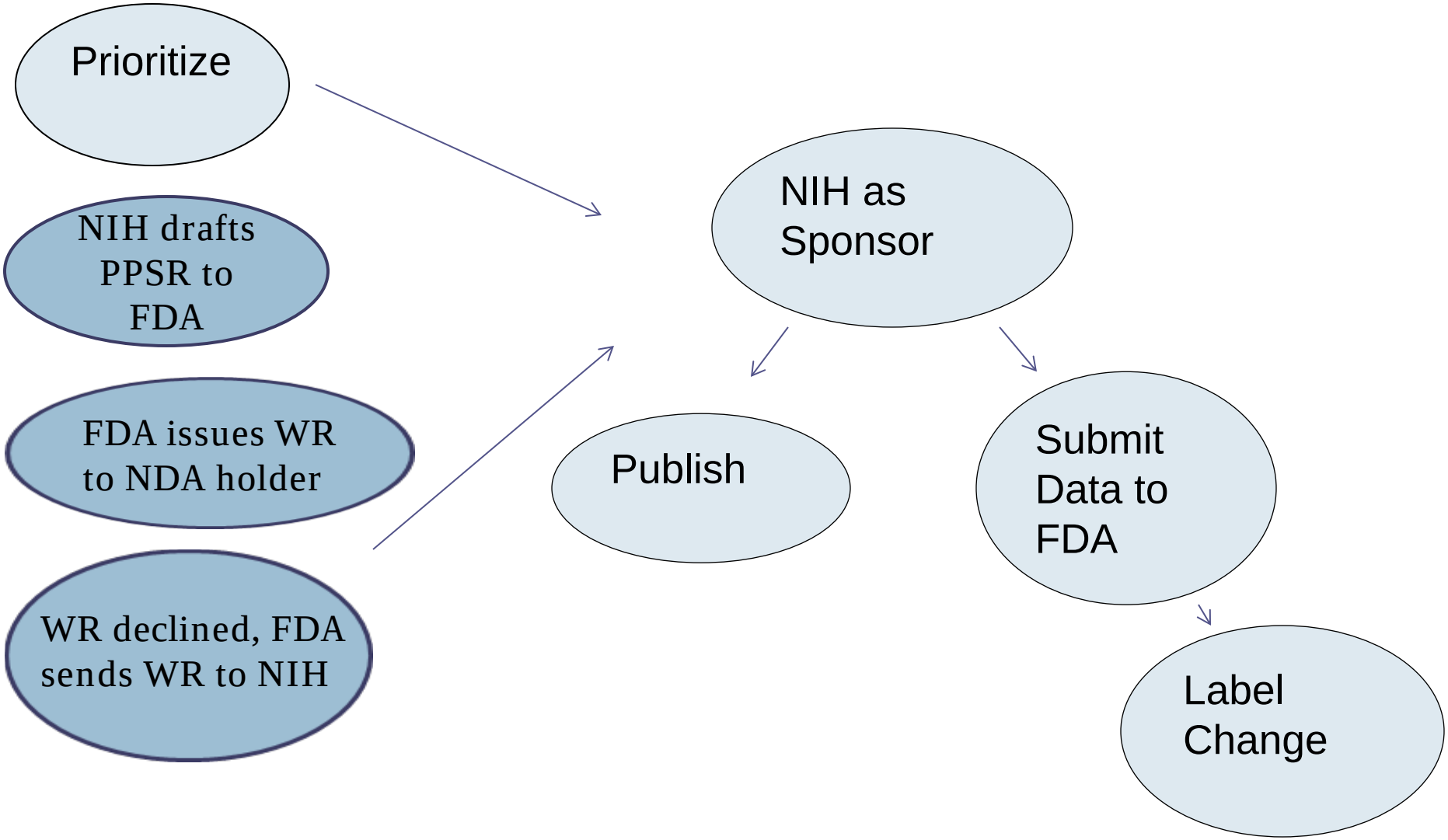
Consultation with experts in pediatric practice and research

Develop, prioritize, publish an Annual List of Therapeutic Areas and Specific Needs

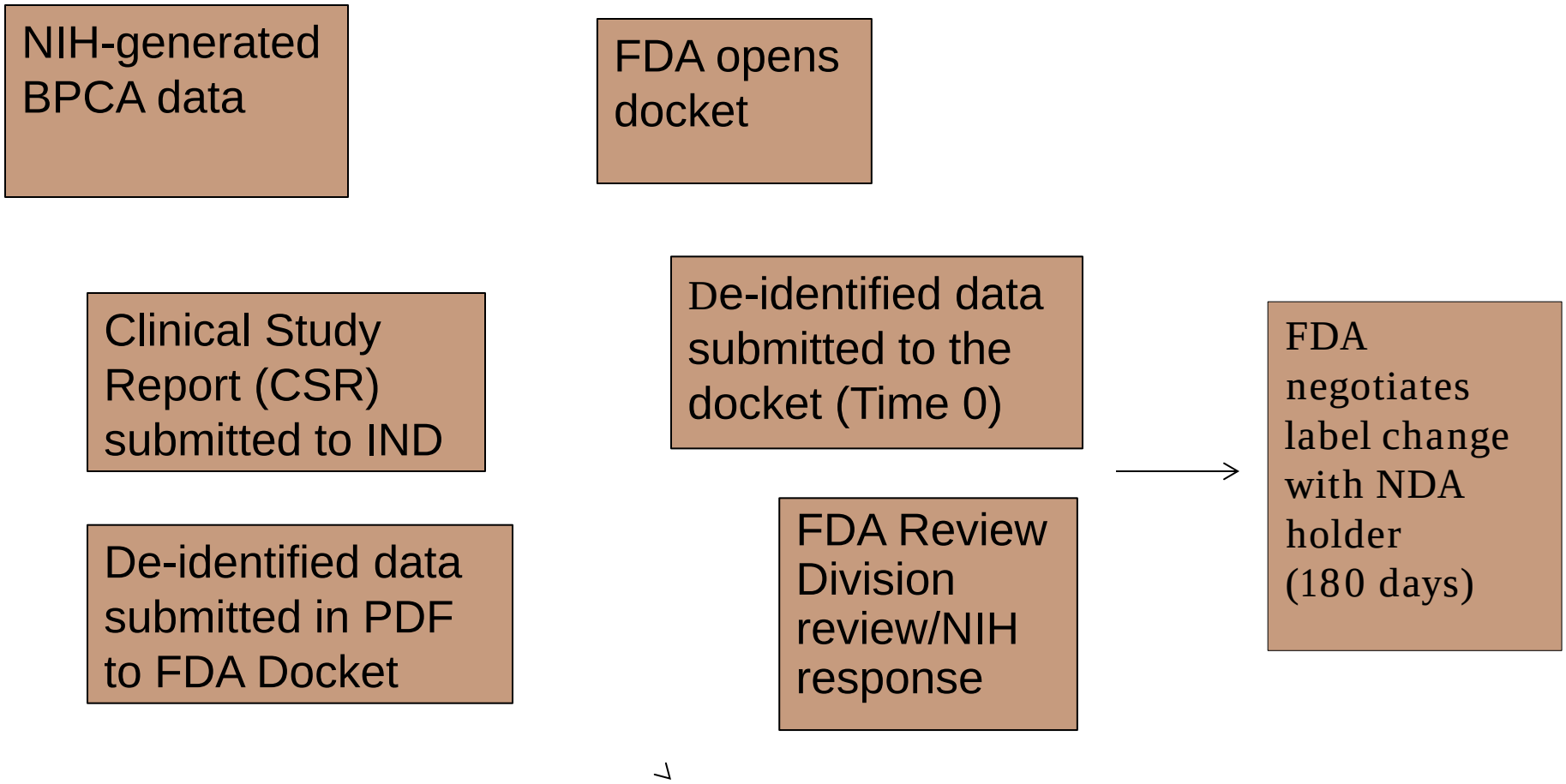
Prioritized Therapeutic Areas

Cardiovascular Disease	Hypertension, Hypotension, Dyslipidemia
Respiratory Disease	Asthma, Pulmonary Hypertension
Infectious Diseases	MRSA, General Infections, Tinea capitis, Tuberculosis, Parasitic Infections, Influenza
Psychiatry	ADHD, Bipolar Disease, Safety of Atypical Antipsychotics
Adolescent Medicine	General therapeutic needs, Over the counter meds
General Pediatrics	Corticosteroids, Cold and Cough Medicines, *Constipation
Formulations	Technology advances
Oncology	Neuroblastoma, Leukemia, Solid Tumors, Formulations
Neurology	Cerebral Palsy, Migraines, Seizures
Intensive Care	Anesthesia, Sedation
Dermatology	Atopic Dermatitis, Severe inflammatory skin disease, Hemangiomas
Rheumatology	Connective tissue disorders
Bio-defense research	Nerve agent exposure, Organophosphate poisoning, Cyanide toxicity
Renal Diseases	Acute kidney injury, Anemia
Hematology	Sickle Cell Disease, Thrombosis
Rare diseases/Endocrine	Fragile X, Type-1 Diabetes, Formulations
Gastroenterology	GE Reflux, Cholestatic disease, Cyclic vomiting, *IBD
Neonatology	BPD, Pain, Neonatal abstinence syndrome, NEC
Special considerations	Intellectual and developmental disabilities
	Pediatric Formulations, Devices

NIH BPCA Process



BPCA Data Submission Process from NIH to FDA



Why Is This Novel?

- NIH and **pediatric stakeholders** can determine which products are in need of labeling changes
- Sponsor: NIH, not pharma
- Label owner: pharma, not NIH or FDA
- FDA negotiates the new pediatric labeling with pharma
- Neither FDA or investigators can put information into a label without sponsor agreeing. This process says the sponsor must come to the table.

Sodium Nitroprusside

- Pediatric Use: Efficacy in the pediatric population was established based on adult trials and supported by the dose-ranging trial (Study 1) and an open label trial of at least 12 hour infusion at a rate that achieved adequate MAP control (Study 2) with pediatric patients on sodium nitroprusside. No novel safety issues were seen in these studies in pediatric patients.

Label

- The effects of sodium nitroprusside to induce hypotension were evaluated in two trials in pediatric patients less than 17 years of age. In both trials, at least 50% of the patients were pre-pubertal, and about 50% of these pre-pubertal patients were less than 2 years of age, including 4 neonates. The primary efficacy variable was the mean arterial pressure (MAP).
- There were 203 pediatric patients in a parallel, dose-ranging study (Study 1). During the 30 minute blinded phase, patients were randomized 1:1:1:1 to receive sodium nitroprusside 0.3, 1, 2, or 3 μg/kg/min. The infusion rate was increased step-wise to the target dose rate (i.e., 1/3 of the full rate for the first 5 minutes, 2/3 of the full rate for the next 5 minutes, and the full dose rate for the last 20 minutes). If the investigator believed that an increase to the next higher dose rate would be unsafe, the infusion remained at the current rate for the remainder of the blinded infusion. Since there was no placebo group, the change from baseline likely overestimates the true magnitude of blood pressure effect. Nevertheless, MAP decreased 11 to 20 mmHg from baseline across the four doses (Table 1).
- There were 63 pediatric patients in a long-term infusion trial (Study 2). During an open-label phase (12 to 24 hours), sodium nitroprusside was started at ≤0.3 μg/kg/min and titrated according to the BP response. Patients were then randomized to placebo or to continuing the same dose of sodium nitroprusside. The average MAP was greater in the control group than in the sodium nitroprusside group for every time point during the blinded withdrawal phase, demonstrating that sodium nitroprusside is effective for at least 12 hours.
- In both studies, similar effects on MAP were seen in all age groups.

Meropenem

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Safety

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MedWatch The FDA Safety Information and Adverse Event Reporting Program

- Safety Information
- Safety Alerts for Human Medical Products
- Drug Safety Labeling Changes

Resources for You

- Merrem I.V. (meropenem for Injection) Prescribing Information, December 2014

Merrem (meropenem) I.V. for injection

Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER) --

December 2014

Summary View

ADVERSE REACTIONS

Adverse Reactions from Clinical Trials

*revisions to adverse reactions in pediatric patients and addition of information from the pediatric study

USE IN SPECIFIC POPULATIONS

Pediatric Use

*addition of pediatric patients less than 3 months of age with complicated intra-abdominal infections

Evelyne Jacqz-Aigrain. *Editorial Commentary*: Effectiveness or Efficacy: Which Study to Evaluate Antibiotics in Neonates?

Clin Infect Dis. 2012 Dec;55(11):1503-4.

- Additional data on efficacy will be provided by 2 studies called NeoMero 1 and NeoMero 2 (NTC01551394 and NT015544124, respectively), both conducted in Europe in infants <90 days of age with bacterial meningitis or late-onset sepsis. At completion date (estimated to be July 2014), meropenem will have a complete and very informative evaluation in neonates, conducted step by step, based on a population PK study, the intermediate effectiveness and safety evaluation published today, a randomized controlled trial for efficacy in neonatal sepsis, and additional PK data in neonatal meningitis. This will hopefully allow a marketing authorization for meropenem in neonates for the treatment of suspected or proven infection, including complicated forms (intra-abdominal infection, meningitis), but obtained >15 years after marketing authorization in infants.
- Therefore, the question remains of how to evaluate antibiotics in neonates: **Is a randomized controlled trial (RCT) always required for an effective and safe use of antibiotics in neonates or to receive a marketing authorization?**

Meropenem label

http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c15e88d3-d903-4e7a-f683-e29f51afa848#ID_0e62c58c-9673-41ab-ac35-1e302d654c23

Pediatric Patients Less Than 3 Months of Age

For pediatric patients (with normal renal function) less than 3 months of age, with intra-abdominal infections, the MERREM I.V. dose is based on gestational age (GA) and postnatal age (PNA). (See dosing table below). MERREM I.V. should be given as intravenous infusion over 30 minutes.

Recommended MERREM I.V. Dosage Schedule for Pediatric Patients Less than 3 Months of Age with Complicated Intra-Abdominal Infections and Normal Renal Function		
Age Group	**Dose (mg/kg)**	**Dose Interval**
Infants less than 32 weeks GA and PNA less than 2 weeks	20	Every 12 hours
Infants less than 32 weeks GA and PNA 2 weeks and older	20	Every 8 hours
Infants 32 weeks and older GA and PNA less than 2 weeks	20	Every 8 hours
Infants 32 weeks and older GA and PNA 2 weeks and older	30	Every 8 hours

There is no experience in pediatric patients with renal impairment.

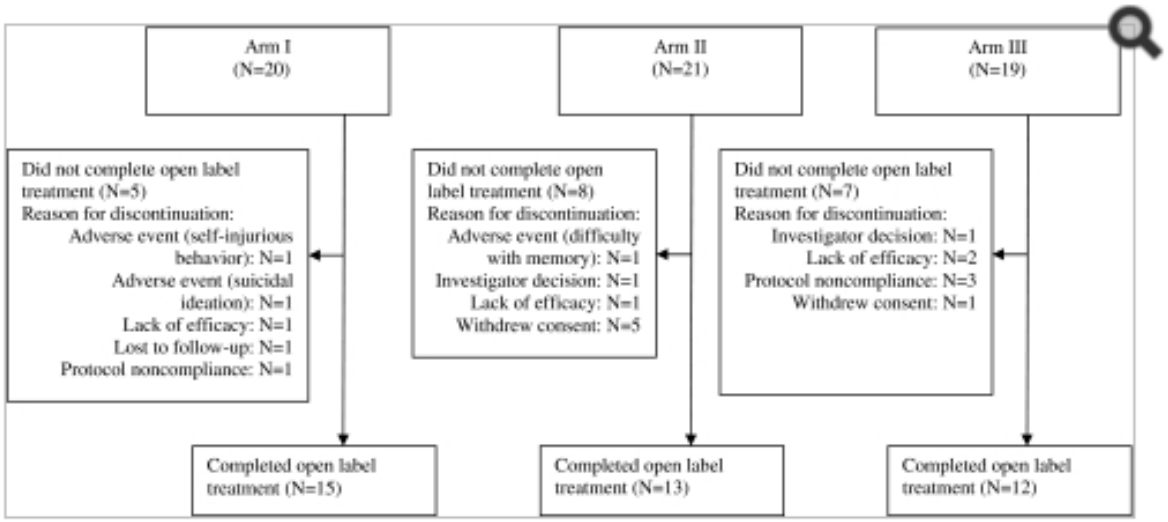
Meropenem label

Table 2 Meropenem Pharmacokinetic Parameters in Patients Less Than 3 Months of Age*

	GA less than 32 weeks PNA less than 2 weeks (20mg/kg every 12 hours)	GA less than 32 weeks PNA 2 weeks or older (20mg/kg every 8 hours)	GA 32 weeks or older PNA less than 2 weeks (20mg/kg every 8 hours)	GA 32 weeks or older PNA 2 weeks or older (30mg/kg every 8 hours)	Overall
CL (L/h/kg)	0.089	0.122	0.135	0.202	0.119
V (L/kg)	0.489	0.467	0.463	0.451	0.468
AUC_{0-24} (mcg-h/mL)	448	491	445	444	467
C_{max} (mcg/mL)	44.3	46.5	44.9	61	46.9
C_{min} (mcg/mL)	5.36	6.65	4.84	2.1	5.65
T1/2 (h)	3.82	2.68	2.33	1.58	2.68

*Values are derived from a population pharmacokinetic analysis of sparse data

Findling RL[1], Kafantaris V, Pavuluri M, McNamara NK, McClellan J, Frazier JA, Sikich L, Kowatch R, Lingler J, Faber J, Rowles BM, Clemons TE, Taylor-Zapata P
Dosing strategies for lithium monotherapy in children and adolescents with bipolar I disorder.
J Child Adolesc Psychopharmacol 2011 Jun;21(3):195-205.



Participant accountability.

Wang WC, Ware RE, Miller ST, et al. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG).
Lancet 2011;377(9778):1663–72

Findings

96 patients received hydroxycarbamide and 97 placebo, of whom 83 patients in the hydroxycarbamide group and 84 in the placebo group completed the study. Significant differences were not seen between groups for the primary endpoints (19 of 70 patients with decreased spleen function at exit in the hydroxycarbamide group *vs* 28 of 74 patients in the placebo group, p=0·21; and a difference in the mean increase in DTPA glomerular filtration rate in the hydroxycarbamide group versus the placebo group of 2 mL/min per 1·73 m^2, p=0·84). Hydroxycarbamide significantly decreased pain (177 events in 62 patients *vs* 375 events in 75 patients in the placebo group, p=0·002) and dactylitis (24 events in 14 patients *vs* 123 events in 42 patients in the placebo group, p<0·0001), with some evidence for decreased acute chest syndrome, hospitalisation rates, and transfusion. Hydroxyurea increased haemoglobin and fetal haemoglobin, and decreased white blood-cell count. Toxicity was limited to mild-to-moderate neutropenia.

Hydroxyurea

Isotretinoin

Vincristine, Actinomycin-D

- Relationship of dose, PK, age and other parameters to veno-occlusive disease
- Studies:
  - Line-clearing method
  - PK
  - Chart review to gather PD data on neurotoxicity, hepatotoxicity; dosing, demographics
  - PK-PD modeling

Neonatal Research Network: Pilot study to treat neonatal hypotension

(Batton BJ et al. J Peds 2012; 161:65-69)

- Design: factorial (hydrocortisone/ dopamine)
- Results: 366 infants screened, 10 enrolled
- Issues: eligibility (indomethacin contra-indicated with HC), consent

Validating Endpoints for Neonates with "Hypotension"

- Questions:
  - How is BP measured in the NICU?
  - Have these methods been standardized or validated in this population?
  - What is a normal neonatal BP at a given gestational or postnatal age?
  - What is the definition of hypotension?
    - Value – systolic/diastolic/mean BP
    - "Perfusion"
    - Shock
    - Oliguria or anuria
  - What is the clinical endpoint in the treatment of hypotension?
  - How is this endpoint measured?

Batton B et al. Evolving blood pressure dynamics for extremely preterm infants. J Perinatol 2014; 34:301-305

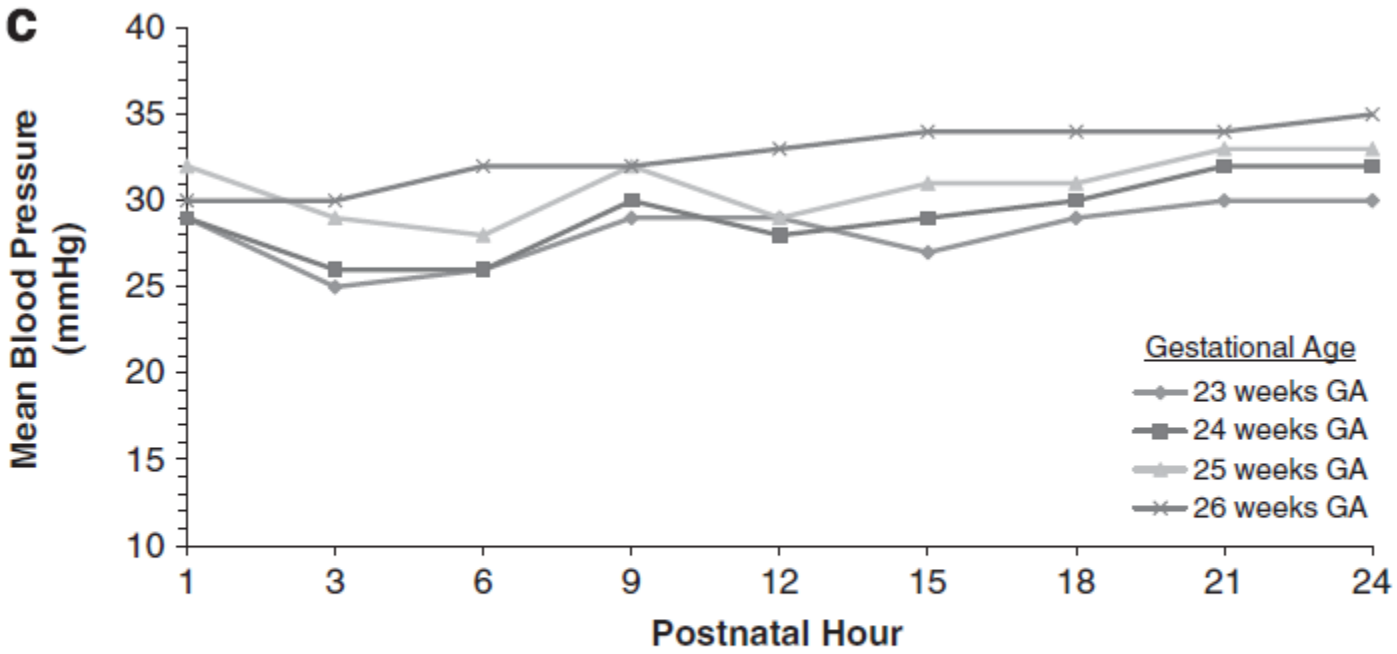
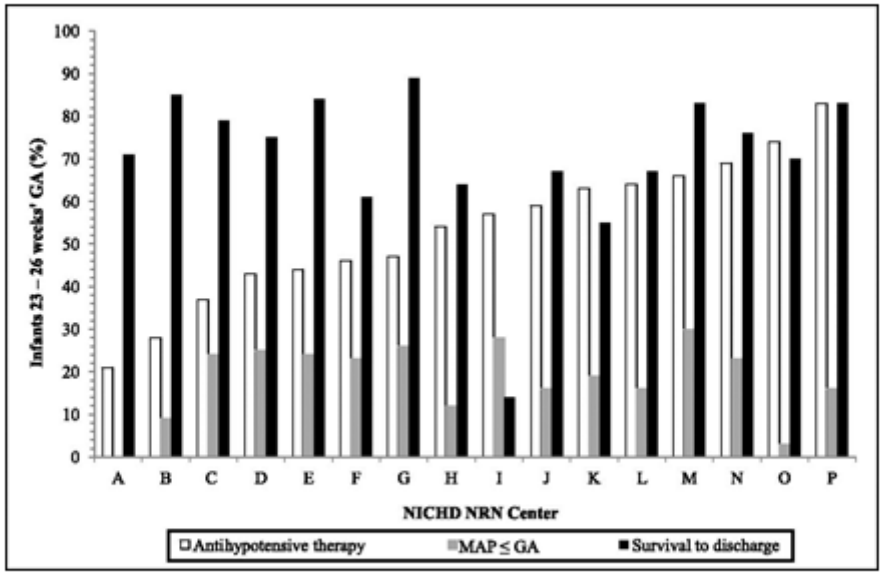


Figure 2. Gestational age-specific changes in the systolic (**a**), diastolic (**b**) and mean (**c**) arterial blood pressure 50th percentile curves over the first 24 h.

Center variation in the rate of antihypotensive therapy administration, frequency of low BP, and incidence of hospital survival.



Beau Batton et al. Pediatrics 2013;131:e1865-e1873

PEDIATRICS®

Electronic Health Records: HRSA co-fund

- AAP Pediatric Research in the Office Setting (ePROS) Comparative Effectiveness Research through Collaborative Electronic Reporting (CER2) network
- Data collections on use, adverse events related to asthma and second generation antipsychotic medications

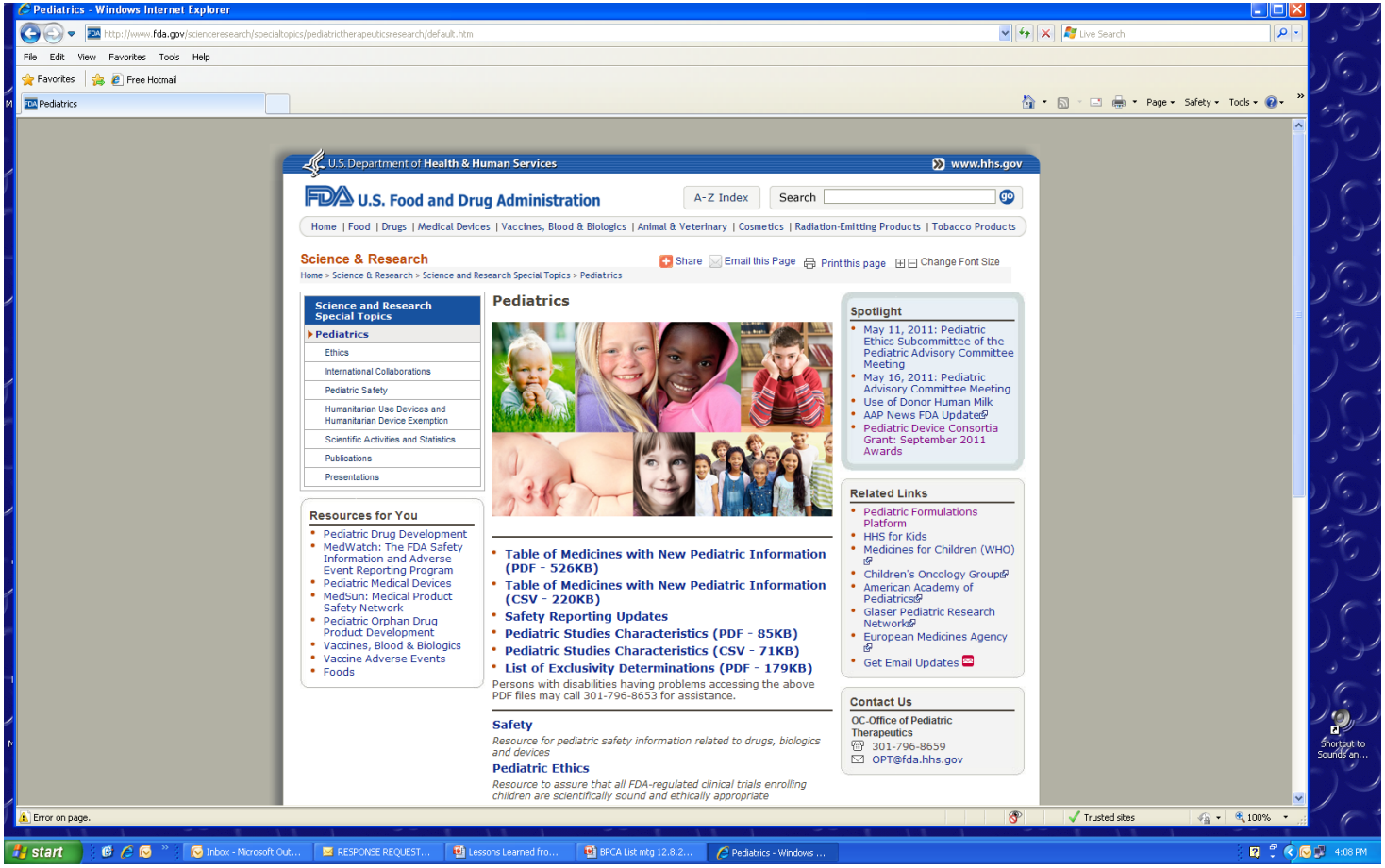
Formulations

- Continual problem with lack of pediatric formulations
  - Excipients
  - IV volumes
  - Oral dosage forms

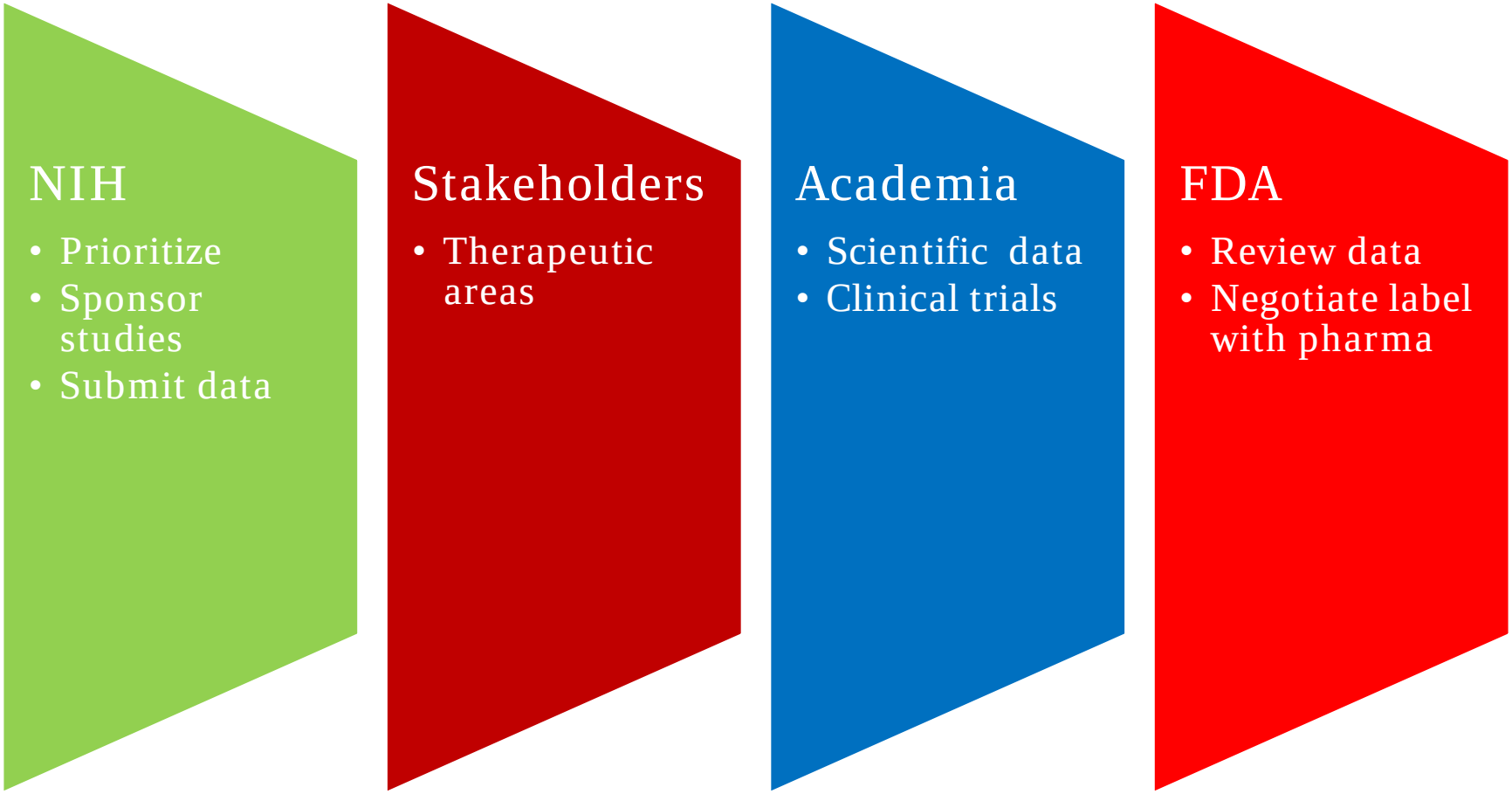
NIH-FDA Formulations Platform Intra-Agency Agreement

- Purpose: Develop an approach for producing oral dosage forms of various BCS class drugs, that are: stable in heat and humidity, tasteless/taste masked, preferably solid orally dissolvable dosage forms, in clinically useful dosage increments
- http://bpca.nichd.nih.gov/collaborativeefforts/initiatives/index.cfm

NIH-FDA Formulations Platform Inter-Agency Agreement



Collaborative Efforts



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